REMARKS

Applicant uses the paragraph numbering of the office action in responding to the Examiner's comments. Claim recitals of CRM197 have been replaced with the more generic term of diphtheria toxoid, support for which is provided at *e.g.*, p. 28, line 19. No claim amendment should be construed as acquiescence in any ground of rejection.

¶¶5-6. CRM197 is described as a species of diphtheria toxoid in WO 99/027944 incorporated by reference in the present specification at p. 13, line 5. Nevertheless, this term has been deleted in favor of the more generic term diphtheria toxoid.

¶7. Priority claim

Priority of certain claims was denied based on the term CRM197. Although applicant disagrees with this determination, the issue is moot in view of the deletion of this term. All pending claims are entitled to a priority date of at least May 26, 2000. Applicant reserves the right to show an earlier date of invention should this prove relevant in this or other proceedings.

¶8. The anticipation rejection of claims 125-127, 129-130, 138-140 and 142-143 over Arumugham is moot in view of claim amendments. The rejection was applied only against claims reciting CRM197 on the basis that such claims were not entitled to priority. Those claims now recite that the carrier is diphtheria toxoid. Those claims are entitled to a priority date of at least May 26, 2000. Therefore, Arumugham is not prior art to those claims.

¶9. Claims 119, 121-125, and 131 stand rejected as allegedly obvious over the combination of Selkoe, Wong and Penney. Selkoe is alleged to teach use of fragments of about 8 or more amino acids of Aβ for immunization to generate antibodies for use in detection. Wong is alleged to teach a conjugate of Aβ1-10 to keyhole limpet hemocyanin to generate an antibody to Aβ for use in detection. Wong is acknowledged not to teach Aβ 1-7 or linking an Aβ fragment to a pathogenic bacterium. Penney is alleged to teach use of carriers such as keyhole limpet

hemocyanin and toxoids from pathogenic bacteria. The Examiner alleges that it would have been obvious to combine Selkoe's teaching of about 8 amino acids with Wong's teaching of Aβ1-10 to arrive at Aβ 1-7 for the benefit of making more antibodies to Aβ for use in diagnosis. The Examiner further alleges that it would have been obvious to substitute KLH with CRM197 as Penney teaches that a heterologous peptide can be used to increase immunogenicity. This rejection is respectfully traversed.

Wong discusses KLH as a carrier for an Aβ fragment for immunization of laboratory animals as a means to generate antibodies. Wong provides no indication that immunization with Aβ has any therapeutic application in humans.

Penney teaches that KLH is a preferred carrier for animal use (*see e.g.*, col. 5, lines 2-4). By contrast, Penney teaches that toxoids from pathogenic bacteria are suitable and commonly used for human use (*see e.g.*, col. 2, lines 5-8; col. 5, lines 4-12).

It would not have been obvious to replace Wong's use of KLH in animals with a toxoid from a pathogenic bacteria because Penney teaches that Wong was already using the preferred carrier for animal use. Wong provides no indication of a potential human use that would have suggested any compensating benefit for foregoing the preferred carrier for animal use in favor of a carrier suitable for human use. Without any indication of a human use by Wong, the purported switch from KLH to a toxoid from a pathogenic bacterium appears to reflect impermissible hindsight reconstruction of the claimed invention.

Furthermore, the combination of Wong and Selkoe would not have motivated selection of an antibody binding to an epitope within residues 1-7 of Aβ. As shown in Table 16 of the present application, such antibodies are particularly advantageous in clearing Aβ deposits in a transgenic mouse model and in an *ex vivo* assay. The purported selection of Wang is not based on recognition of this or other advantage of such an antibody, but an impermissible hindsight reconstruction resulting from selective reliance on only part of the art.

Although Wong discusses an antibody binding within residues 1-10 of Aβ, he does not provide any reason to think that this antibody is any better for diagnosis than any other antibody to Aβ. Wong's selection of an antibody to the first ten residues of Aβ can be rationalized from the perspective that the full sequence of Aβ was not available at the time, and

the first ten residues were most likely to be free from error due to amino acids being identified starting with the N-terminus. Consistent with this view residue 11 of the Alzheimer's Aβ sequence shown by Wong is wrong (Gln instead of Glu). In the passage of time between Wong and the effective filing date of the present application, the full-and correct sequence of Aβ became well-known and many antibodies were generated to various parts of the molecule (*see, e.g.*, Iwatsubo, *Neuron,* 13:45-53 (1994) discussing C-terminal antibodies (cited in the IDS filed February 6, 2007 as cite no. 192); and WO90/12871, reporting stronger staining with antibodies to a 17-24 epitope (cited in the IDS filed February 6, 2007 as cite no. 85). Viewing the art in its totality, there was no reason to select Wong's antibody rather than any of the numerous other antibodies to Aβ subsequently described in the art for diagnosis.

Selkoe casts additional doubt on the proposition that Wong's antibody would have been selected based on advantages in diagnosis. Selkoe reports that antibodies raised against amyloid deposits showed stronger staining than an antibody to a synthetic peptide (*see* column 21, lines 13-26). Thus, if diagnosis from detecting Aβ were one's goal, and one were to have relied only on Wong's and Selkoe's teaching, one would presumably have selected an antibody raised against Aβ deposits rather than Wong's antibody to a synthetic peptide.

Selkoe also does not suggest replacing Wong's antibody with an antibody binding to an epitope within residues 1-7 of Aβ. A fair reading of Selkoe's comment that a fragment of about 8 or more residues can be used for generating antibodies is that a fragment of 8 residues is about the minimum size and that if a smaller fragment is used there is at least a risk of failure. There is no apparent reason in either Wong or Selkoe that the artisan would have felt compelled to test the limits of fragment size and risk possible failure in generating an antibody rather than following the protocol of Wong (who used an Aβ1-10 fragment) or Selkoe who used an Aβ1-28 fragment. Furthermore, even if the artisan had the fortitude to test the boundaries of feasibility of fragment size, there would have been no reason for him to select an Aβ1-7 fragment, rather than an Aβ 2-8, or Aβ3-9 fragment or indeed any other seven amino acid fragment from Aβ.

For these reasons, it is respectfully submitted that the combination of Wong and Selkoe did not provide any teaching that would have led the artisan to select an Aβ1-7 fragment as an immunogen.

Because it was not obvious to modify Wong either by using an Aβ 1-7 peptide or replacing KLC with a toxoid from a pathogenic bacteria, withdrawal of the rejection is respectfully requested.

¶10. Claims 119-125 and 131-132 stand rejected as allegedly obvious over the combination of Selkoe, Wong and Penney in father view of Restifo. Restifo is alleged to teach using multiple copies of a peptide as an immunogen. Claims 119-125 and 131-132 would have been nonobvious for at least the same reasons as discussed above.

¶11. Claims 119, 121-124, 131 and 133-138 stand rejected as allegedly obvious over the combination of Selkoe, Wong and Penney in further view of Hancock. Hancock is alleged to teach use of QS21 as add adjuvant. The Examiner alleges it would have been obvious to use QS21 as an adjuvant in view of Hancock alleged teaching that it is particularly effective in eliciting antibodies. The distinctions discussed above are equally applicable here. In addition, Hancock would not have motivated replacement of Freund's adjuvant used by Wong in favor of QS21.

Hancock discusses QS21 in the context of a vaccine against a virus - RSV - intended for human administration. RSV is not a self-antigen such as Aβ. QS21 is indicated to enhance stimulation of antibodies relative to alum (an adjuvant commonly used in humans) or relative to no adjuvant (*see e.g.*, col. 3, lines 3-7). However, QS21 is not indicated to improve stimulation of antibodies relative to Freund's adjuvant, the adjuvant used by Wong. Freund's adjuvant is the most commonly used adjuvant for animal administration (Harlow & Lane, Antibodies: A Laboratory Manual (CSHL 1988)) at p. 98 and is characterized as a "potent immunostimulant" but restricted to animal use (Penney paragraph bridging cols. 2-3). Also, the stimulation reported by Hancock is only in the context of antibodies against RSV and it would have been unclear whether QS21 would have been advantageous even relative to alum in other contexts. Absent any recognition of potential administration of Aβ to humans by Wong, a report that one adjuvant suitable for human use was better than another in the context of an RSV

vaccine would not have been seen as relevant to Wong's goal of generating antibodies to Aβ in a laboratory animal.

¶12. Claims 119, 121 and 133-143 stand rejected as allegedly obvious over the combination of Selkoe, Wong, Penney, Hancock and Collier. Collier is alleged to teach fusion of an immunogen to CRM197. This rejection is traversed for at least the reasons given in ¶11 above.

¶13. Claims 119-143 stand rejected for alleged nonstatutory obviousness-type double patenting over claims 403, 406, 409, 412, 415, 419 and 422 of US Application No. 10/583,503. Before consideration can be given to the issue of double patenting, two or more applications must have at least one common inventor and/or common assignment (*see* MPEP §804). However, there are no common inventors between the applications and the assignment is also different (the present case is assigned to Elan Pharma International Ltd., and the cited case is assigned to Elan Pharmaceuticals, Inc.[1] and Wyeth). Therefore, a obviousness-type double patenting rejection is improper.

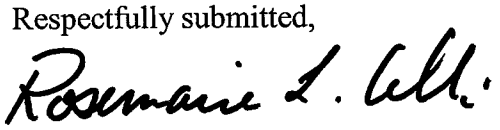
¶14. Present claims 119-143 and claims 403, 406, 409, 412, 415, 419 and 422 of US Application No. 10/583,503 are not directed to the same invention. The cited claims from '503 application specify additional specifics of conjugation not present in the present claims. Therefore, declaration of an interference would not be appropriate notwithstanding different assignments.

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

[1] Elan Pharmaceuticals, Inc. is under an obligation to assign the instant application to Elan Pharma International Limited.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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